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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. 85N-0214
Proposed Rule - 180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications
64 Fed. Reg. 42,873 (Aug. 6, 1999)

Dear Sir or Madam:

TEVA Pharmaceuticals USA would like to take this opportunity to provide comments on the above-referenced proposed rule. The specific provisions of the proposed rule on which we will comment are set forth below as excerpts, followed by TEVA's position and the rationale behind the position.

TEVA endorses the underlying goals expressed by FDA in the preamble to the proposed rule, namely "to provide an incentive for challenging a listed patent, while at the same time preventing prolonged or indefinite delays in the availability of generic drug products" (64 Fed. Reg. at 42,874). Such delays, as FDA is aware, harm not only the specific generic applicants whose products are kept off the market, but also the consumers and payers forced to pay higher drug prices due to delays or limitations in generic competition. These delays also result in unintended windfalls to innovator companies.

TEVA, along with much of the generic drug industry, has also looked to this new rule making for an additional benefit, namely clarification of the regulatory situation. It is difficult, if not impossible, for industry to plan, develop, and bring to market generic drug products in the face of the currently unpredictable and constantly changing rules of the game.

We recognize that the agency has made every effort to provide a document that ensures these objectives are accomplished. Unfortunately, in our view, the proposal falls far short of accomplishing its goals in a number of important ways.

In particular, TEVA believes it is critical for any new regulations on 180-day exclusivity to be firmly grounded in the statute. FDA's current proposal fails this test in a number of key respects, as described in more detail below. If the new rule making does not stand on firm legal ground, it will inevitably be overturned in court, plunging both industry and FDA into another prolonged period of

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uncertainty and confusion, wasting a valuable opportunity to restore much-needed balance and predictability, and wreaking further havoc in precisely the area of most importance, namely the timely market entry of generic drugs.

The following comments will specifically describe the shortcomings of the proposed rule, as well as certain individual issues on which TEVA endorses the positions taken by the agency. Where appropriate, we will also propose alternatives to achieve the important policy goals noted above.

A. 180-Day Exclusivity Eligibility

1. Only First Applicant is Eligible

Although the agency has considered alternative interpretations, such as "rolling exclusivity" in which the next-in-line applicant is eligible for exclusivity should the previous applicant become ineligible, FDA proposes to maintain the current interpretation.

[T]here is one exception to this principle. If the agency accepted for filing a substantially complete ANDA prior to the NDA holder's submission of a late (untimely) filed patent, the ANDA applicant is not required to certify to this patent. However, if the ANDA applicant amends its ANDA to include a paragraph IV certification to the untimely filed patent, and the ANDA applicant later withdraws that paragraph IV certification, the next applicant to file a paragraph IV certification to the untimely filed patent will be eligible for exclusivity. The agency believes that in this situation it is appropriate to grant exclusivity to an applicant who was required to file a paragraph IV certification because the applicant filed its ANDA after the NDA holder submitted the patent information. (64 Fed. Reg. at 42,875)

TEVA agrees conceptually with the agency's proposal not to implement rolling exclusivity since, in general, rolling exclusivity serves to delay competition and the entry of generic products to market.

However, with regard to the single circumstance in which FDA proposes to permit rolling exclusivity, TEVA believes clarification is needed. FDA states that where a first ANDA applicant has voluntarily included in its already filed ANDA a paragraph IV certification to a late-listed patent, and later withdraws that certification, an applicant who submitted its ANDA after that untimely patent was listed, and who therefore was required to file a paragraph IV certification to the patent, should still be eligible for exclusivity. The problem with this approach is that it appears to ignore the applicant whose ANDA was not first, but was also accepted for filing before the listing of the untimely patent, and who voluntarily amended its application to include a paragraph IV certification to the untimely patent and then did <u>not</u> later withdraw that certification. Presumably FDA does not

mean to permit the later applicant who does not even submit its ANDA until after the untimely patent lists to obtain exclusivity at the expense of these earlier (but not first) applicants. TEVA therefore suggests that FDA add a further proviso to this exception, such as "so long as no previous applicant still maintains a paragraph IV certification to the relevant patent."

In order for an ANDA to be considered substantially complete for the purposes of exclusivity, the bioequivalence studies submitted in the ANDA at the time it is initially submitted must, upon review by the agency, meet the appropriate standards for approval. If the applicant must conduct a new bioequivalence study to obtain approval of the ANDA, the application will not be considered to be substantially complete and the applicant will not be eligible for exclusivity. Id.

TEVA disagrees with this part of the proposed rule. There are many unforeseen circumstances that may lead to the conduct of a new bioequivalence study which are outside the applicant's control, or which do not necessarily mean that the original submission was incomplete. Changing agency requirements, the development of new and possibly important technologies, and the impact of petitions submitted by other companies, are among the circumstances that could lead to the need to re-do biostudies or perform new biostudies. As long as the first applicant continues to actively pursue its application and its litigation, that applicant should not be penalized in such a situation. Rather, companies using their best scientific judgement to pursue the optimal means of developing a bioequivalent product should be supported and encouraged to pursue such activity aggressively, submit ANDAs early, and have a meaningful opportunity to benefit from potential exclusivity.

Moreover, it is, for all practical purposes, impossible to make business plans and decisions if eligibility for exclusivity is not conclusively determined until the bioequivalence review has been completed. Litigation strategies – and the associated risks and costs – are determined very early in the process. For this reason it is critical that eligibility for the 180-day exclusivity also be definitively determined as early as possible. Accordingly, TEVA believes that an application that is substantially complete for acceptance for filing is also substantially complete for purposes of exclusivity, and it is FDA's responsibility to determine "completeness" for this purpose in a timely manner.

[I]f the first applicant submits a new paragraph IV certification because, for example, it makes a formulation change requiring a supplement or an amendment to its ANDA, it may no longer be accorded first applicant status. Id.

TEVA does not agree with this provision of the proposed rule. Its net result would be to limit the flexibility of the first applicant in countering the strategies of the patent holder/NDA holder during litigation. This would likely compromise that applicant's legal position, and result in significant unfairness to the applicant. Under this proposed policy, a new paragraph IV certification necessitated by, for instance, a newly listed patent, or a change in formulation by the NDA holder, could jeopardize the first applicant's eligibility for exclusivity. This policy would therefore hand

NDA holders a weapon they could use to effectively nullify 180-day exclusivity for any drug and render successful patent challenges impossible – an outcome clearly at odds with the policy of preserving incentives for such challenges.

If the ANDA applicant submitting the first substantially complete ANDA with a paragraph IV certification submits paragraph IV certifications to multiple patents at that time, any of those certifications will render the applicant eligible for exclusivity. The first court decision finding one of the patents invalid, not infringed, or unenforceable will trigger the running of the applicant's exclusivity. Id. at 42,876.

While TEVA holds the position that exclusivity attaches to the drug product rather than to an individual patent, and therefore agrees that any one of multiple paragraph IV certifications is sufficient to render the first applicant eligible for exclusivity, we do not agree that the exclusivity clock should start with the first court decision finding one of the patents invalid, not infringed or unenforceable. Very often, patents are listed sequentially in order to draw out the brand's exclusive marketing. Thus, starting the generic exclusivity clock with the decision on the first patent means that the exclusivity may well run while the later listed (but not untimely) patents are still being litigated. In addition, it can be expected in many cases that the weaker patents will be disposed of in litigation ahead of the stronger patents, either by summary judgment or otherwise. In that scenario, a court decision disposing of a weaker patent would start the exclusivity clock, forcing the first applicant either to sit out (and thus waste) its exclusivity period, or go to market at risk from the stronger patents that are still being litigated.

Thus, this policy would potentially deny the first applicant the rewards of its exclusivity period while it is still taking risks and funding litigation against the patent holder. This is at odds with the intent of Congress, which was to provide protection to the patent challenger by starting the 180-day clock at the time of the court decision or of commercial marketing, rather than approval, thus avoiding pressure on the patent challenger to take undue marketing risks in order to preserve its exclusivity benefit. By the same token, this structure also, not incidentally, protects the intellectual property rights of the patent holder by allowing for orderly generic market entry following final disposition of the relevant patent rights. Accordingly, to preserve this intent, TEVA proposes that a court decision on the last **limiting** patent – *i.e.*, the court decision that clears the final patent-related legal barrier to marketing – be the decision that starts the clock.

TEVA also believes the agency should make clear that the 30-month stay of effective approval contemplated by section 505(j)(5)(B)(iii) of the act can apply only to the first paragraph IV ANDA to a particular drug, in keeping with the structure and intent of the statute. This would avoid situations where the patent holder can delay generic competition (and, in the process, manipulate different generic applicants' right to exclusivity) by listing patents successively one at a time and thereby triggering 30-month stays that begin long after the notice of patent challenge is received on the first paragraph IV ANDA.

5. Patent Expiration and 180-Day Exclusivity

The agency is clarifying that once the patent for which the first applicant filed a paragraph IV certification expires, the first applicant is no longer eligible for exclusivity. Id. at 42,877.

TEVA is in full agreement that exclusivity should not run beyond the life span of the patent, or be based on an expired patent. Once the patent has expired, there can no longer, by definition, be any "challenge" to that patent. Moreover, the first applicant who, in effect, simply waits out the patent (even though that applicant may have initially submitted a paragraph IV application) has not really risked or accomplished anything in terms of benefitting subsequent generic applicants or the public. And, in the most practical sense, allowing exclusivity to be based on an expired patent is certain to further impede and delay generic market entry, frustrating the underlying goal of the statute.

B. The Results of the Patent Challenge

1. Triggering Period

The agency is proposing the use of a 180-day "triggering period," during which there must either be a favorable court decision regarding the patent or the first applicant must begin commercial marketing of its product. If neither of these events occurs during the triggering period, the first applicant will lose its eligibility for exclusivity and subsequent ANDA's will be eligible for immediate approval. Id.

TEVA strongly opposes the proposed triggering period for several reasons, the main reason being its lack of foundation in the statute, which will render the provision an easy target for court challenge. While we appreciate the intent behind the proposal of this triggering period, *i.e.*, to avoid excessive delays in the availability of generic products, it is not difficult to imagine a deluge of law suits when triggering periods threaten first applicants' enjoyment of a full six months of exclusive generic marketing. Even companies that may support the triggering concept in principle will be disadvantaged if they do not challenge their own threatened loss of exclusivity under these circumstances. The resulting likely judicial invalidation of this concept will only throw the 180-day exclusivity situation back into the same kind of legal chaos created by the invalidation of the "successful defense" rule (which, arguably, had a better claim to statutory consistency than the proposed triggering period) in Mova v. Shalala, 140 F.3d 1060 (D.C. Cir. 1998). It is critical that the agency not thus fritter away the opportunity this rulemaking presents to restore order and predictability to the 180-day exclusivity scheme, and to thereby accomplish the goal of timely generic market entry and cost competition.

The threat of the triggering period also puts needless pressure on the first applicant to launch its product at the risk of treble damages. In this way the applicant is pressured to give up the protection from such damages that is intended and afforded under the statute. FDA's assumption that the first

applicant can somehow "obtain" a court decision within the 180-day triggering period grossly overestimates the degree of control a defendant in a patent infringement lawsuit can exercise over the court process.

To replace the triggering period, TEVA suggests two parallel approaches, both well-grounded in the statute: (1) a closer monitoring of the Orange Book to ensure listing of only those patents that are appropriate, specifically compound patents and use patents covering the first approved use of the product, and (2) proper application of the statutory provision on declaratory judgement actions.

First, exercising proper control over the listing of patents in the Orange Book would be a major step toward limiting the circumstances under which paragraph IV challenges are needed in the first place. This would in turn reduce the incidence of needless delays in generic market entry due to abuses of the 180-day exclusivity by first paragraph IV filers, either individually or in conjunction with other companies. It would also facilitate earlier generic market entry by reducing the frequency of paragraph IV litigation and the resulting 30-month stay of approval. And it would accomplish this without undermining the incentive value of the 180-day exclusivity in cases where that exclusivity is truly merited – unlike the agency's triggering period proposal. To accomplish this, the agency should return to its original policy of listing in the Orange Book only compound patents and method of use patents that refer to the first approved use of the product. This would also make it much more likely that patent challenges would be focused on invalidity – and thus truly would create the potential of clearing the path to market for all generics, which was the original concept underlying the compensatory offer of 180-day exclusivity to the applicant that accomplished that goal – rather than non-infringement, which typically benefits only the individual applicant that has successfully designed around the patent.

In this connection, FDA should also require patent and/or NDA holders who wish to list patents to certify separately, in connection with the submission of a patent for listing (either as part of a marketing application or otherwise), that the patent in question does actually cover the drug that is the subject of the relevant NDA or an approved method of using that drug, on pain of civil and/or criminal sanctions for fraudulent certification. FDA is charged by law with the responsibility of ensuring that all submissions to it, including patents for listing, are truthful and accurate, and the agency should not shirk this responsibility.

Second, accepting the ability of an applicant to start the 180-day clock by obtaining a "case or controversy" dismissal in a declaratory judgment action would also provide an important means of preventing a first paragraph IV filer from abusing its position to block generic market entry. The courts have accepted TEVA's position that such a dismissal, where it has the legal effect of estopping the patent holder from enforcing the patent against the generic drug applicant, is the functional equivalent of a court decision holding the patent to be not infringed and/or unenforceable against that applicant, and is therefore a court decision that starts the 180-day exclusivity period.

TEVA Pharmaceuticals USA, Inc. v. FDA, 182 F.3d 1003 (D.C. Cir. July 20, 1999), followed on remand, No. 99-67 (D.D.C. Aug.. 19, 1999). FDA should likewise accept this eminently sensible, statutorily based, and judicially endorsed interpretation.

D. Settlement Agreements

The proposed regulations, by applying the triggering period, would reduce the delay in market entry of generic drug products that can result from such agreements. Although agreements may still be made, their effect on generic competition would be limited by the requirement that, within 180 days of the first tentative approval of a subsequent ANDA, the first ANDA applicant begin commercially marketing its own product or obtain a favorable court decision. Id. at 42,880.

As TEVA has already stated, we do not support the triggering period provisions of the proposed rule. As an alternative, in order to reduce the delays in market entry of generic drug products caused by settlement and licensing agreements between innovator and generic drug companies, TEVA proposes that FDA require the first ANDA applicant to notify the agency immediately of any settlement or other agreement between the first ANDA applicant and the patent owner or NDA holder that has the effect of precluding the patent/NDA holder from enforcing its patent against that applicant. Where such settlements oblige the first applicant to amend its certification from a paragraph IV to a paragraph III, under the correct interpretation announced by FDA in this proposed rule (but unfortunately not currently followed by the agency), the first applicant will automatically lose its eligibility for exclusivity, so that the settlement will not operate to block subsequent applicants from the market. However, where such a settlement does not result in a change from a paragraph IV certification to a paragraph III, for whatever reason, it should be treated as a triggering event for the 180-day exclusivity period, because by definition it has the same practical effect as a court decision of invalidity, non-infringement, or unenforceability – *i.e.*, it means that the blocking patent has been removed as a legal obstacle to the marketing of the generic drug product.

H. Waiver of 180-Day Exclusivity and Relinquishing Eligibility

Proposed §314.107(e) would permit the ANDA applicant that has obtained 180 days of exclusivity with the occurrence of a triggering event . . . to notify FDA during the period of exclusivity that it will waive its exclusivity in favor of a subsequent ANDA or ANDA's containing a paragraph IV certification.

It should be noted that an applicant may selectively waive its exclusivity only after the 180-day exclusivity period has begun to run with the occurrence of one of the triggering events. . . . Before that time, the first applicant is only eligible for exclusivity and might not obtain exclusivity if, for example, it failed to trigger the exclusivity before the expiration of the triggering period.

Prior to the occurrence of a triggering event, the first applicant may relinquish its eligibility for exclusivity entirely, and by so doing would permit the agency to approve immediately any subsequent ANDA's that are eligible for approval. It may not, however, waive its exclusivity in favor of a specific applicant(s). Id. at 42,881.

TEVA is in favor of all aspects of the agency's proposal with regard to the waiver of 180-day exclusivity. In particular, TEVA notes that allowing a first applicant to selectively waive its exclusivity to another company prior to the occurrence of a triggering event would serve to encourage sham applications submitted for the purpose of acquiring a "right" to exclusivity that could then be traded away, without any bona fide intent to bring a patent challenge to completion and/or to commercially market the drug. For this reason, TEVA agrees strongly that until a first applicant's potential right to exclusivity is perfected through the occurrence of a triggering event, that applicant should not be allowed to sell such a right. However, mechanisms should be in place to allow a company to make the necessary arrangements in advance for the ultimate waiver of exclusivity, to become effective once the exclusivity period begins.

I. Multiple Strength/Drug Product Exclusivity

The agency has determined that each strength of a drug product can be independently eligible for exclusivity. Applicants may be eligible for a separate exclusivity period for each particular strength of the drug product in an ANDA when each strength refers to a different listed drug. Id.

TEVA fully agrees with this approach and with the agency's reasoning in support of it. Not only is this approach consistent with the statutory definition of a drug product, but it will also encourage the submission of ANDAs covering the greatest possible number of strengths, and prevent an applicant who applies for only one strength from blocking the market to generic competition in other strengths of the drug. Thus, this approach will promote the earliest market entry of the greatest number of strengths of a particular drug.

At the same time, TEVA urges FDA to take the necessary steps toward administrative modifications to permit an applicant to actually realize exclusive marketing on one or more strengths of a product that are tied to the review of an ANDA containing other strengths as to which that applicant is not eligible for exclusivity. TEVA is aware of a number of ANDAs currently pending approval for which different companies are eligible for exclusivity on different strengths. Therefore, administrative modifications to clarify the situation and allow applications to move expeditiously to final approval with exclusivity, where appropriate, are imminently necessary. Here again, clarification of the process is integral to the successful market entry of generic drug products. TEVA believes it is essential for the agency to be proactive in communicating which products will be eligible for final approval and exclusivity, and when. Uncertainty about such critical factors makes it impossible to launch generic drug products in a timely manner.

III. Proposed Implementation Plan

The agency proposes that any final rule based on this proposal take effect 30 days after its publication in the Federal Register. The agency proposes to apply the provisions of any final rule to ANDA's pending as of the effective date and to ANDA's that are submitted after that date. Id. at 42,882.

TEVA strongly disagrees with the agency's proposal to apply the provisions of the final rule to ANDA's pending as of the effective date and to all ANDA's that are submitted after that date.

First, the strategies adopted in the development and submission of ANDA's up to the effective date of the final rule will be based on the agency's current policy of regulating directly from the statute and the precedents set under this policy. It would be unfair to apply new policies retroactively to these ANDA's. Additionally, it would create an unlevel playing field to apply different sets of rules to applications for the same product, depending upon whether the application was submitted before or after the effective date of the final rule. For these reasons, TEVA proposes that the final rule be applied only to ANDA's submitted after the effective date of the rule, and only to those ANDA's for which a previous paragraph IV application has not been submitted prior to the effective date of the rule.

TEVA appreciates this opportunity to comment on the proposed rule and trusts that these comments are well-taken. We look forward to the finalization of the rule in the hope that it will restore the balance of benefits and protection that was the intent of statute.

Sincerely,

Deborah Jaskot

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